

Phase III microbicide trial methodology: opinions of experienced expanded safety trial participants in South Africa

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ABSTRACT

In preparation for effectiveness trials of candidate vaginal microbicides, scientists are debating trial design and implementation challenges, including choice of control arm(s), product-sharing across arms, and visit schedules. This study involved a survey of South African women participating in an expanded safety trial of the candidate microbicide Carraguard gel. The first 100 consenting women who attended the study clinics in Ga-Rankuwa and Gugulethu (total $N = 200$) were interviewed; all women had been using a study gel for at least 6 months at the time of the interview. The study found that many participants thought that including a condoms-only arm would result in increased product-sharing, male partner resistance to trial participation and decreased enrollment; no clear patterns emerged regarding the potential effect on condom use and cohort retention. The majority of women preferred a monthly visit schedule, would be willing to use a product for 2 years, and thought that their product use would not decrease over time. Thus flexibility in trial design and implementation strategies is needed until evidence-based decisions can be made. When including a condoms-only arm, extra efforts should be made to explain the importance of all study arms to potential participants and to measure adherence and product-sharing.

Keywords: microbicides, HIV prevention interventions, randomised controlled trials.

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RÉSUMÉ

Au cours des préparatifs des épreuves d'efficacité de candidat des microbicides vaginaux, les scientifiques discutent les défis de la conception et l'exécution d'une épreuve, entre autres, le choix de bras commandé, un bras de partage de produit et les visites prévues. Cette étude a nécessité une enquête auprès des femmes sud-africaines participant à l'épreuve de sûreté augmentée du gel candidat microbicide Carraguard. La première centaine de femmes consentantes qui assistaient à l'étude clinique de Garankuwa et de Gugulethu ($N = 200$ au total) ont subi des entretiens: toutes les femmes utilisaient le gel d'étude pendant une période de 6 mois au moment de l'entretien. L'étude a démontré que beaucoup de participants étaient de l'avis que l'ajout d'un bras seulement-condoms aurait pour conséquence une hausse de partage de produit, la résistance à la participation des partenaires masculins et la baisse des inscriptions; il n'y a pas eu d'émergence de tendances claires concernant l'effet potentiel sur l'utilisation du préservatif et la rétention de cohorte. La majorité de femmes ont préféré une visite mensuelle, elles seraient prêtes à utiliser le produit au cours d'une période de 2 ans et elles estimaient que leur utilisation du produit ne va pas diminuer entre-temps. De ce fait, il faut une flexibilité de stratégies de la conception et l'exécution de l'épreuve jusqu'à ce que des décisions basées sur preuves soient prises. Lorsqu'on ajoute le bras seulement-condoms, on doit faire davantage d'efforts pour expliquer l'importance de tous les bras d'étude aux participants potentiels et de mesurer l'adhésion et le partage de produit.

Mots clés: microbicides, interventions de prévention au VIH, épreuves commandées randomisées.

Introduction

Currently available HIV prevention tools are limited and not feasible for many women (van de Wijgert, & Coggins, 2002). The need to expand the range of HIV prevention tools available, especially those that women can use, is urgent. Microbicides are products that are applied topically inside the vagina or rectum to prevent infection with HIV, and potentially other sexually transmitted infections (STIs). They could be formulated as gels, creams, suppositories, or vaginal rings; they could be contraceptive or not; and they could be used alone or in combination with a physical barrier. According to the Alliance for Microbicide Development, about 29 candidate products are in the pipeline in 2005. Of these, 14 are in active pre-clinical development, 9 are in phase I and II safety trials, and 6 in phase IIb/III effectiveness trials (Alliance for Microbicide Development, 2005). South Africa is actively involved in microbicide development and hosts many microbicide trials.

Scientists are still debating the most appropriate control arm for microbicide effectiveness trials: a matching placebo arm, a no-product/condoms-only arm, or both in parallel (Jones, van de Wijgert, & Kelvin, 2003; Kilmarx, & Paxton, 2003; Padian, 2003; Stein, Myer, & Susser, 2003). A matching placebo arm allows for blinding, which in turn yields the most unbiased estimate of product efficacy. However, even though a placebo typically does not contain the active ingredient

of the candidate microbicide, it may nonetheless have some anti-HIV effects (for example, due to its lubricating and/or physical barrier properties) and/or local toxicity. In a condoms-only arm, women would not receive a vaginal product, but they would receive the currently available HIV prevention package in a clinical trial setting. Using a condoms-only arm would allow for comparisons between 'best case scenario HIV prevention plus microbicide' and 'best case scenario HIV prevention without microbicide'. The disadvantage of a condoms-only arm, however, is that it cannot be blinded, which may result in differential behaviour changes (for example, more condom use in the condoms-only arm), lower enrollment and retention rates in the condoms-only arm, and increased product-sharing between participants receiving a test product and those not receiving a test product. Having both types of control arms in parallel would allow for blinding between the microbicide and matching placebo arms, may allow the researchers to measure the effect of the matching placebo on HIV acquisition and local toxicity, and would allow for comparisons between the microbicide arm and each control arm. However, the disadvantage of having two control arms is that the sample size of the trial increases, raising concerns about feasibility and cost.

Optimal trial duration and visit schedules in phase III trials are also being debated. The trial duration should

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be such that primary endpoints will be maximised, but durable treatment effect and long-term safety can also be assessed. Current proposals range from 6 to 24 months of follow-up per participant. Some scientists have decided to follow the majority of participants for a relatively short period of time (6 – 12 months) but to follow a subset of participants for a longer period. Visit schedules need to be frequent enough to determine the timing of HIV seroconversions, and yet not so often as to burden the women participating, local trial staff and the overall trial budget.

Microbicide trial procedures typically include medical examinations, counselling, and interviewing. All medical procedures have to be carried out by licensed clinicians (physicians and/or nurses). Counselling and interviewing could be done by these same clinicians, but is often done by non-medically trained staff. In some cases, each participant is counselled and interviewed by the same staff member to optimise rapport-building and efficiency. In other cases, each participant is counselled and interviewed by different staff members in an effort to minimise courtesy bias.

In this paper we describe the results of a survey among South African women who were participating in an expanded safety and acceptability trial of the candidate vaginal microbicide Carraguard (Population Council, New York). At the time of the survey, all women had been using a study gel for at least 6 months. We asked their opinions regarding a variety of phase III trial design and implementation issues to inform future phase III trial designs.

Materials and methods

A double-blind, randomised, placebo-controlled expanded safety and acceptability trial of Carraguard gel was conducted at two sites in South Africa: Ga-Rankuwa near Pretoria and Gugulethu, Cape Town. Each site enrolled 200 HIV-negative, non-pregnant, healthy women between June 2000 and November 2001; half of the women were randomised to Carraguard gel and the other half to a matching placebo gel (methylcellulose gel). Women were asked to insert one applicator of study gel 3 times per week (with or without sex), and to use study gel with condoms every time they had sex. Both gels came in identical single-use Micralax applicators (Norden Pac International AB, Kalmar, Sweden), which were packaged into boxes of 12. Women were asked to

return to the study clinic for a minimum of 6 and a maximum of 12 scheduled visits with approximately 1 month between visits. At each study visit, participants underwent HIV counselling, a blood draw for HIV testing, a pelvic examination including sampling for a variety of reproductive tract infections, a face-to-face interview, and re-supply of condoms and gel applicators (they were given a minimum of 24 applicators per visit). Participants were told that they could come back to the clinic at any time to obtain additional supplies as needed.

The first 100 consenting women who attended each of the study clinics between August and October 2001 as part of this expanded safety trial participated in a phase III feasibility survey ($N = 200$). They were interviewed about experiences with gel supply and sharing in the expanded safety trial and opinions about hypothetical phase III study. The results from this survey were linked to screening data from the expanded safety trial for baseline demographics and sexual behaviour.

The interviewers were women who spoke the local language, and were not members of the expanded safety trial staff. All interviews were conducted in a private room at each study site according to a structured questionnaire. The questionnaire was translated into Setswana (Ga-Rankuwa) and Xhosa (Gugulethu) and back-translated into English. Data were double-entered and managed in Microsoft Access 2000 (Microsoft Corporation, Redmond, Washington). Open-ended text variables were coded by two independent research assistants, compared, and discrepancies were resolved. Data were analysed using SPSS software version 10.0 (SPSS Inc., Chicago, Illinois). Reported p values are two-sided Fisher's exact test for categorical variables and ANOVA t -test for continuous variables.

Ethical approvals were obtained from the ethical review committees of the University of Cape Town, the Medical University of Southern Africa and the Population Council.

Results

The mean age of the survey participants was 28 years, ranging from 18 to 55. The majority of the women (87%) had a steady partner, but only 17% were married. Of those with a husband or steady partner, 72% were not living with this partner, and 74% were

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either unsure or thought that this partner had other partners. Differences in baseline demographic and sexual behavior characteristics were seen between the two sites. The women in Ga-Rankuwa were, on average, slightly younger and had completed more school. More women in Ga-Rankuwa reported condom use and regular vaginal cleansing, and fewer reported cigarette smoking and current use of family planning (see Table 1).

The 200 survey participants had enrolled in the expanded safety trial an average of 10 months prior to the feasibility survey (ranging from 6 to 15 months). Average duration since enrollment at the time of the survey was slightly longer for interviewees from Gugulethu (11.1 months) than Ga-Rankuwa (10.3 months, $p = 0.013$).

The survey participants thought that some women in their communities may not have wanted to participate in the expanded safety trial because they were not interested in the study gel (41% thought that this was very likely), they were worried that the gel might cause health problems (51%), they were worried that

the gel might cause relationship problems (63%), or their male partner did not approve (53%) (Table 2). Most of them thought that not wanting to be tested for HIV (82%) and not wanting to be asked about sexual behaviour (72%) were other very likely reasons why some women chose not to participate.

Only a handful of interviewees at each study site reported that they had been asked for, had given, or had received study gel from other participants during the expanded safety trial (Table 2). Eleven per cent reported to have been asked for study gel, but only 4% had given study gel to relatives or friends. The majority of interviewees thought that none or hardly any women had shared gel with others during the trial, but 23% in Ga-Rankuwa and 11% in Gugulethu thought that some gel-sharing had occurred ($p = 0.054$).

Table 3 shows opinions regarding a condoms-only control arm. All questions were asked after the interviewer had explained what a condoms-only control arm is, and how a three-armed trial (Carraguard, placebo and condoms-only arms) would differ from the two-armed expanded safety trial

TABLE 1. BASELINE DEMOGRAPHIC AND BEHAVIOUR CHARACTERISTICS OF PHASE III FEASIBILITY SURVEY PARTICIPANTS (FROM EXPANDED SAFETY TRIAL SCREENING DATA), SOUTH AFRICA, 2001

	Ga-Rankuwa % (N = 100)	Gugulethu % (N = 99)*	Total % (N = 199)*	p-value
Mean age in years (range)	26.9 (18 - 44)	29.0 (18 - 55)	28.0 (18 - 55)	0.048
Mean years of school completed (range)	9.4 (3 - 14)	7.9 (0 - 10)	8.7 (0 - 14)	< 0.001
Mean number of live births (range)	1.2 (0 - 6)	1.5 (0 - 6)	1.4 (0 - 6)	0.069
% working	14	14	14	1.000
% married or has steady partner	84	89	87	0.293
% living with husband or steady partner (among women currently with steady partner; N = 173)	30	27	28	0.737
% has any other partners	9	8	8	1.000
% report yes/don't know steady partner has other partners (among women currently with a steady partner; N = 174)	69	78	74	0.235
% used condoms in last year with steady partner (among women who had steady partner; N = 187)	67	53	59	0.054
% used condoms in last year with other partners (among women who had other partners; N = 52)	69	31	40	0.022
% currently uses modern method of family planning	78	92	85	0.009
% cleansed the vagina regularly prior to joining expanded safety study [†]	49	19	34	< 0.001
% currently smokes cigarettes	4	21	13	< 0.001

*One case was not linkable, resulting in 199 women with complete data.

[†]Reported in feasibility survey, not screening data from expanded safety trial.

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TABLE 2. REPORTS ON REASONS FOR NON-ENROLLMENT AND GEL SHARING BY SITE, SOUTH AFRICA, 2001

	Ga-Rankuwa % (N = 100)	Gugulethu % (N = 100)	Total % (N = 200)	p-value
Thought that it was very likely that other women did not participate because:				
• they were not interested in study gel	26	56	41	< 0.001
• they were worried gel may cause health problems	44	57	51	0.147
• they were worried gel may cause relationship problems	55	71	63	0.064
• their male partner did not approve	50	56	53	0.348
• they did not want to be asked questions about their sexual behaviour	72	71	72	0.812
• they did not want to get tested for HIV	83	81	82	0.215
Was ever asked for study gel by other participants	1	7	4	0.065
Was ever asked for study gel by friends or relatives	10	12	11	0.822
Ever gave study gel to other participants	0	1	1	1.000
Ever gave study gel to friends or relatives	4	4	4	1.000
Ever received study gel from someone else	0	1	1	1.000
Ever threw study gel away	1	3	2	0.621
In your opinion, how many women shared study gel with others?				
• None or hardly any women	77	89	83	
• Some/about half the women	21	10	16	0.054
• Most/all or almost all women	2	1	2	

(Carraguard and placebo arms). When asked how they would feel if they were assigned to a condoms-only arm, more than half the women at each site said that they would not like it, but only 14% said that they would not participate as a result. About a third of the women (34% in Ga-Rankuwa and 26% in Gugulethu; $p = 0.031$) reported that they thought that their partner would object to their participation if assigned to a condoms-only arm. The majority of interviewees thought that some women would decline to participate if assigned to a condoms-only arm, with only 5% in Ga-Rankuwa and 14% in Gugulethu reporting that none or hardly any women would decline to participate ($p = 0.014$). Forty-five per cent of women thought that gel-sharing would increase in the context of a condoms-only arm, but 30% thought it would decrease and 22% thought it would stay the same. When asked what would happen to their own condom use if assigned to a condoms-only arm, 43% of the women said that they would use condoms more often, 19% less often, and 36% would not change their condom use. Responses were different between the two sites, with 58% of women in Gugulethu reporting that they would use condoms more often compared with 28% in Ga-Rankuwa ($p < 0.001$). The main reasons cited implied that if women would not have access to study gel, they would rely more on condoms for protection against HIV. If assigned to the condoms-only arm, 31% of the women would stay in the study

shorter, 25% longer, and 43% for the same amount of time. When asked what they thought would happen to other women's condom use and retention in the context of a condoms-only arm, women reported similar opinions.

Table 4 shows opinions and preferences regarding trial duration and visit schedule. The majority of women (91%) reported that they would be willing to use study gel for as long as 2 years. Most interviewees reported that their gel use had stayed the same (66%) or increased (26%) during their participation in the expanded safety trial. Similarly, they predicted that their gel use would stay the same (55%) or would increase (32%) if asked to use it for 2 years. The majority of women would prefer a monthly study visit schedule including pelvic examination (86%), as opposed to bimonthly, quarterly or biannual study visits, even if they were assigned to the condoms-only arm (80%). They would be even more willing to return to the study clinic regularly for 2 years if waiting times at the clinic were reduced (81%), better food and drink were offered during the clinic visit (82%), and more monetary transport compensation were offered (87%). Only about a third of the women said that they would be more willing to return regularly if the visits involved fewer medical exams, less counselling or less interviewing (data not shown).

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TABLE 3. OPINIONS ABOUT A CONDOMS-ONLY CONTROL ARM BY SITE, SOUTH AFRICA, 2001

	Ga-Rankuwa % (N = 100)	Gugulethu % (N = 100)	Total % (N = 100)	p-value
What would best describe your feelings if assigned to no-gel arm?				
• Would not matter to me	45	35	40	0.084
• Would not like it but would still participate	36	53	44	
• Would not like it and would not participate	16	11	14	
• Would not want to participate for other reasons	3	1	2	
Partner would object if enrolled in no-gel arm	34	26	30	0.031
In your opinion, how many women would decline to participate if assigned to no-gel arm?				
• None or hardly any	5	14	10	0.014
• Some/about half	52	33	42	
• Most/all or almost all	38	43	40	
• Don't know	5	10	8	
In your opinion, how many women in no-gel arm would try to get gel from other women?				
• None or hardly any	28	33	30	0.007
• Some /about half	46	26	36	
• Most/all or almost all	23	29	26	
• Don't know	3	12	8	
If there was a no-gel arm, do you think gel sharing would				
• Decrease	30	31	30	0.660
• Stay the same	25	18	22	
• Increase	42	48	45	
• Don't know	3	3	3	
If assigned to no-gel arm, would you use condoms				
• Less often	25	13	19	< 0.001
• The same	44	28	36	
• More often	28	58	43	
• Don't know	3	1	2	
In your opinion, how many women in no-gel arm would use condoms				
• Less often	31	15	23	0.059
• The same	34	43	39	
• More often	33	39	36	
• Don't know/no response	2	3	2	
If assigned to no-gel arm, would you stay in study for				
• Shorter period of time	25	36	31	0.001
• The same amount of time	56	30	43	
• Longer period of time	19	31	25	
• Don't know	0	2	1	
In your opinion, would women in no-gel arm stay in study for				
• Shorter period of time	47	54	50	0.331
• The same amount of time	37	27	32	
• Longer period of time	11	16	14	
• Don't know	5	3	4	

Table 5 shows that the majority of women (87%) felt comfortable being counselled and interviewed about condom use by the same study staff person. When asked for their preference, 30% of women said that they would prefer being counselled and interviewed by separate persons, 36% by the same person, and 34% had no preference. Reasons for these preferences are listed in Table 5.

Discussion

The survey results provide useful insights about a variety of phase III design and implementation dilemmas from the perspective of experienced South African microbicide trial participants. However, the following three limitations should be noted. First, the interviewees are not likely to be representative of the general population, due to the stringent eligibility

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TABLE 4. STUDY DURATION AND VISIT SCHEDULE PREFERENCES BY SITE, SOUTH AFRICA, 2001

	Ga-Rankuwa % (N = 100)	Gugulethu % (N = 100)	Total % (N = 200)	p-value
Gel use compared with when participant first started the study (N = 199)				
• Less often	9	8	9	0.900
• The same	67	65	66	
• More often	24	27	26	
Willing to use study gel for 2 years	91	90	91	0.806
Describe gel use over 2-year time period (N = 198)				
• Would use gel more often the longer I am in study	20	45	32	< 0.001
• Gel use would not change during the study	69	41	55	
• Would use gel less often the longer I am in study	9	7	8	
• Would not be willing to use gel for 2 years	2	6	4	
• I don't know	0	1	1	
Which visit schedule would you prefer the most?				
• Clinic visit and exam monthly	87	85	86	0.459
• Clinic visit monthly and exam bimonthly	3	5	4	
• Clinic visit and exam bimonthly	5	3	4	
• Clinic visit bimonthly and exam quarterly	3	1	2	
• Clinic visit and exam quarterly	1	1	1	
• Clinic visit quarterly and exam biannually	1	5	3	
Would still be willing to visit study clinic as often if assigned to no-gel arm	84	76	80	0.192

criteria for the expanded safety trial, and the fact that these women had successfully used a study gel for an average of 10 months at the time of the interview. Secondly, many of the questions we asked were hypothetical in nature. Data collected through hypothetical questioning often do not correlate well with data based on actual experiences (Elias & Coggins, 2001). Lastly, the presence of courtesy bias

cannot be ruled out, even though precautions were taken – for example, the interviewers were not part of the regular expanded safety trial implementation team. However, we think that for many of the questions asked neither the interviewers nor the interviewees knew which answers we wanted to hear. They were not familiar with the subject matter and did not know the opinions of the investigators.

TABLE 5. COUNSELLING AND INTERVIEWING PREFERENCES BY SITE, SOUTH AFRICA, 2001

	Ga-Rankuwa % (N = 100)	Gugulethu % (N = 100)	Total % (N = 200)	p-value
Is comfortable being counselled and interviewed about condom use by the same person	84	90	87	0.217
Prefer to be counselled and interviewed by (N = 199)				
• Separate persons	46	13	30	< 0.001
• Same person	28	44	36	
• No preference	25	43	34	
Reasons for preference – separate persons (women who replied 'separate persons' only, N = 57)				
• More information/more interesting	43	69	49	0.177
• More comfortable/freer with information	25	23	25	
• Other	31	8	26	
Reasons for preference – same person (women who replied 'same person' only, N = 70)				
• Better confidentiality	21	14	17	0.716
• More comfortable with having a relationship with only one person	62	71	67	
• Other	17	15	16	

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More than half of the survey participants indicated that they would not like to be assigned to a condoms-only arm, but only 14% would not participate if they were. Their opinions about the potential effects of including a condoms-only arm in future phase III trial designs on enrollment, gel-sharing and condom use were not always consistent and therefore difficult to interpret. Many – but certainly not all – of the survey participants thought that including a condoms-only arm would result in increased gel-sharing, male partner resistance to trial participation, and decreased enrollment; no clear patterns in opinions emerged regarding the potential effect on condom use and cohort retention. It is important to keep in mind that the survey participants were successful gel users with a positive attitude towards microbicides. They themselves reported that not all women in their communities would have the same level of interest in microbicides. However, it is likely that microbicide trials will continue to attract volunteers who are interested in microbicides, and are therefore likely to be disappointed when randomised to a condoms-only arm. While our data indicate that implementation of a condoms-only arm may be challenging, we believe that it is feasible. For example, Roddy *et al.* successfully completed an open-label phase III effectiveness trial of Nonoxynol-9 (N-9) gel in Cameroon (Roddy, Zekeng, Ryan, Tamoufe, & Tweedy, 2002). In that trial there were no differences between the N-9 gel and condoms-only arms in retention rates and reported sexual behaviour, including condom use.

A 'wishful thinking' effect may have been present in this cohort of microbicide trial participants. Despite state-of-the-art participant education efforts, it is likely that many participants still wanted to believe that they were receiving an active product that is effective against HIV. Many microbicide researchers would agree that wishful thinking is likely to occur in most microbicide trials regardless of trial design, and it is therefore of the utmost importance to identify effective methods of minimising it. Participant education should, for example, include a clear explanation of the importance of all study arms.

Gel sharing in the expanded safety trial appeared minimal, which may have been due to the fact that all participants received a study gel and did not know which gel they received. Forty-five per cent of the interviewees thought that gel-sharing would increase

with a condoms-only arm, while 53% thought that it would stay the same or decrease. When asked differently, 63% of the survey participants thought that a significant number of women in the no-gel arm would try to get gel from women in the gel arms, compared with 31% who thought that none or hardly any of these women would try to get gel. Gel-sharing is potentially a serious problem, which may not be solved by high-quality participant education alone. In the Carraguard expanded safety trial, compliance with gel use was assessed by participant self-reports, and by counting returned used and unused applicators. In future trials, particularly if a condoms-only arm were to be included, we recommend adding additional measurements of adherence and gel-sharing if possible. For example, bar-coding technology could be used to keep track of individual applicators, and biochemical tests to measure adherence could be pursued.

Most interviewees indicated that they preferred a monthly visit schedule (as in the expanded safety trial) as opposed to a bimonthly, quarterly or biannual schedule. These results should be interpreted with caution; women who do not like to visit a study clinic every month would not have enrolled in the expanded safety trial. Moreover, other factors (such as stability of study products, logistics, and cost) are likely to be important in determining visit schedules. The majority of interviewees reported that they used study gel with the same or increasing frequency throughout the expanded safety trial. Almost all of them said that they would be willing to use study gel for 2 years, and that they thought their gel use would not decrease over time. The debate on optimal trial duration is still ongoing, and includes discussions about the trade-off between required sample size and duration of participation per woman, and possible reductions in product use compliance and HIV incidence over time. We did not find a clear pattern in preferences for being counselled and interviewed by the same or separate study staff members. The decision on how to implement counselling and interviewing should therefore mostly be guided by methodological and logistical considerations.

In conclusion, like many others, we believe that flexibility in trial designs and implementation strategies is important until evidence-based decisions can be made about optimal designs and strategies (Foss, Vinckerman, Heise, & Watts, 2003). Several phase III

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effectiveness trials have just started or are about to be fielded. These trials will hopefully result in proof-of-concept, the validation of trial endpoints, and empirical data to evaluate trial designs and implementation strategies.

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